Competitive blocking of matrix metalloproteinases (MMPs) with synthetic peptides in Breast Cancer models

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Introduction: Matrix Metalloproteinases (MMPs) are a family of enzymes that play roles in various physiological and cellular processes, including wound healing, inflammation and tissue remodeling. Dysregulation of MMPs activity is associated with many pathological conditions, including cancer. The use of synthetic peptides can be a strategy to reach or compete for active sites of MMPs. These peptides are generally short sequences derived from natural substrates of MMPs, designed to competitively inhibit their enzymatic activity. Objectives: Synthesize and evaluate the activity of the peptide derived from the TNF? sequence, an ADAM17 substrate peptide (subtADAM17), and evaluate it cellular effect in comparison with TRAP6-peptide that potentially increases the activity of ADAM17. Methods: The synthesis of the subtADAM17 and TRAP6 peptides was carried out using a solid-phase synthesis with Fmoc chemistry. The peptides were evaluated in breast cancer cell lines models at different stages, whereas MCF-7 represents an epithelial early stage model and MDA-MB-231 represents a mesenchymal and advanced stage cancer model. The effects of the treatments were observed based on wound healing assays, Western blotting and Proteomic profiling. Selected proteins that characterize EMT were used to develop a multiplex targeted proteomic panel comprising 49 representative peptides. Results: The proteomic analysis identified approximately 700 proteins in the samples, including well-known biomarkers of tumor progression. Targeted proteomics data enabled us to observe quantitative differential expression between treatments involving synthetic peptides. In the epithelial model, treatment with the TRAP6 peptide resulted in increased proliferative capacity and elevated protein expression, whereas treatment with the subtADAM17 led to a reduction in these biomarkers, along with decreased cell proliferation. Conclusion: Competitive blockade of matrix metalloproteinases such as ADAM17 using synthetic peptides represents a promising approach for inhibiting breast cancer progression and metastasis.

Agradecimentos: